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Author(s)	Fung, JWK; Lam, KSL
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Neurofibromatosis and insulinoma

Joseph WK Fung, Karen SL Lam

Summary

A 45-year-old man with neurofibromatosis presented with recurrent seizures due to hypoglycaemia caused by an insulinoma. The attacks were abolished after the successful removal of the insulinoma. This probably represents another example of the association between neurofibromatosis and a tumour consisting of cells with amine-precursor-uptake and decarboxylation.

Keywords: neurofibromatosis, insulinoma, hypoglycaemia

Neurofibromatosis is well known for its association with a wide variety of tumours involving the nervous system. It has also been shown that neurofibromatosis can occur concomitantly with endocrine tumours such as pheochromocytoma,^{1,2} carcinoid tumour of the small intestine,^{2,3} medullary carcinoma of the thyroid,⁴ and pancreatic somatostatinoma,⁵ suggesting a possible association between neurofibromatosis and tumours consisting of cells with amino-precursor-uptake and decarboxylation (APUD). Co-existence of neurofibromatosis with an insulinoma has not been previously described. We report here a case of an insulinoma presenting with seizure attacks in a patient with neurofibromatosis.

Case report

A 45-year-old man was admitted into the University Medical Unit, Queen Mary Hospital in July 1991 because of generalised convulsion. He was mentally subnormal and lived in a sheltered home. He also had a history of neurofibromatosis since childhood. Further enquiry revealed that he had had recurrent seizure attacks, usually occurring in the early morning, since 1990 despite treatment with phenytoin prescribed at a general medical clinic. There was no history of diabetes mellitus and no possible exposure to oral hypoglycaemic agents or insulin from his room-mates. On examination he was only intelligent enough to obey simple commands. There were numerous dermal neurofibromata all over the body as well like multiple café-au-lait spots and axillary freckles. His blood pressure was 120/80 mmHg. Examination of the other systems revealed no abnormal findings. Routine haematological and biochemical investigations including complete blood counts, liver and renal function test, calcium and phosphate levels were normal.

Fasting hypoglycaemia was documented on three occasions when the plasma glucose fell to 2.2, 2.1 and 2.0 mmol/l, respectively. The corresponding serum insulin levels were not appropriately suppressed, being 49.4, 10.6 and 5.9 μ U/ml, respectively (normal range <20). Serum cortisol (basal and synacthen-stimulated) and thyroxine levels were normal. Electroencephalogram did not reveal any epileptic or focal abnormality. Chest and skull X-ray were unremarkable apart from slight thickening of skull bones over the frontal region and the petrous bone. Computed tomography (CT) scan of the brain showed generalised thickening of skull vault; there was no space-occupying lesion, no abnormal contrast enhancement or calcification. CT scan of the abdomen and pelvis showed that there was no abnormal abdominal mass and the para-aortic and retroperitoneal lymph nodes were not enlarged. CT scan of the pancreas and coeliac angiography showed a suspicious lesion near the junction between the body and tail of the pancreas. To localise the insulinoma further, intra-arterial stimulation with calcium and venous sampling of insulin^{6,7} was performed. Because of technical difficulties, the protocol was modified so that in addition to the cannulation of the hepatic and splenic arteries, the dorsal pancreatic artery was cannulated instead of selective injection into the gastroduodenal and superior mesenteric arteries which would have yielded a more precise tumour localisation. There was a six-fold rise in insulin level in both hepatic veins following calcium injection into the dorsal pancreatic artery suggesting the presence of an insulinoma, which could be in the body of the pancreas. At laparotomy, a 3/4 cm firm nodule was detected on bimanual palpation at the inferior edge of distal body of the pancreas. Intra-operative insulin sampling confirmed this to be the insulinoma with the insulin level distal and proximal to the nodule being 6.02 and 26.80 μ U/ml, respectively, the corresponding insulin level in the portal vein was 20.5 μ U/ml. Intra-operative ultrasonogram showed that there was no other lesion in the pancreas. Enucleation of the tumour was performed. Subsequent histological examination confirmed this to be an islet cell tumour with positive immuno-staining for insulin. Immuno-staining for glucagon and somatostatin were both negative.

Discussion

It is seldom difficult to diagnose the presence of an insulinoma but a high index of suspicion is

Department of
Medicine, University
of Hong Kong, Queen
Mary Hospital, Hong
Kong
JWK Fung
KSL Lam

Correspondence to
Dr KSL Lam

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required. In this patient, the picture was complicated by the patient's intellectual state and the possible association of multiple tumours with neurofibromatosis. The inability of the patient to express his symptoms and his social background rendered it difficult to obtain a good history, accounting for his being treated as simple epilepsy for nearly one year. This case illustrates once again the importance of excluding an underlying cause which includes treatable metabolic disturbances such as hypoglycaemia and hypocalcaemia in all patients presenting with epilepsy.

Secondly, neurofibromatosis is an interesting disease because of its variable association with different kinds of tumours especially of the brain. Any space-occupying lesion in the brain can cause epileptic attack by itself. Also, it is well known that sarcomatous change is not uncommon in patients with a longstanding history of neurofibromatosis. Any retroperitoneal sarcoma by itself can secrete IGF II which can also result in hypoglycaemia and in turn cause epileptic attacks. This latter possibility was excluded by the insulin levels during hypoglycaemia and the radiological investigations.

The association between neurofibromatosis and phaeochromocytoma has long been recognised. More recently, the concomitant occurrence of neurofibromatosis and carcinoid tumours of the intestine has also been described.^{2,3} Up to 1989, 10 cases of duodenal carcinoids producing somatostatin in patients with neurofibromatosis have been reported. Somatostatin-producing tumour in the pancreas has also been described in a patient with neurofibromatosis.⁵ This association between neurofibromatosis and APUD cell tumours was further supported by a case reported by Yoshida *et al*³ in which the concomitant occurrence of duodenal somatostatinoma, medullary thyroid carcinoma and bilateral adrenal medulla hyperplasia was found in a single patient with neurofibromatosis.

In our patient, the co-existence of neurofibromatosis and insulinoma may be purely coincidental. However, in view of the proven association of neurofibromatosis with other APUD cell tumours such as somatostatinoma, phaeochromocytoma and medullary carcinoma of the thyroid, this may represent another example of such an association. It is likely that in time other endocrine tumours such as gastrinoma and glucagonoma may also be found to

Neurofibromatosis

- characterised by multiple skin neurofibromas and pigmentation
- can be divided clinically into type 1 (peripheral) and type 2 (bilateral acoustic or central)
- associates with other tumours such as:
 - skin tumours (subcutaneous nodules, axillary freckles, café au lait spots)
 - neural tumours (cutaneous neurofibroma, eighth nerve sheath neurofibroma, meningioma, glioma (including optic nerve glioma), plexiform neuroma)
 - others (ganglioneuroma, phaeochromocytoma, carcinoid tumour of the intestine)

Insulinoma

- arises in the pancreas from APUD cells
- a pancreatic islet cell tumour that secretes insulin
- confirmed by hypoglycaemia in association with inappropriate and excessive insulin secretion
- associates with other endocrine tumours, particularly parathyroid adenoma, pituitary adenoma, adrenal adenoma and rarely thyroid adenoma, as part of multiple endocrine neoplasias

Learning/summary points

- look for any underlying cause, especially treatable metabolic disturbance, in all patients with epilepsy
- hypoglycaemia may present as grand mal seizures
- insulinoma may be associated with neurofibromatosis

co-exist with neurofibromatosis, because all APUD cell tumours arise from the neural crest and migrate to different parts of the body including pancreatic islets, thyroid, small bowel, stomach, anterior pituitary, adrenal medulla, lung and carotid body. The association between insulinoma and neurofibromatosis is also an important observation because this constitutes another possible cause of seizure attacks in patients with neurofibromatosis.

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